Int. J. Cancer: **94,** 449–455 (2001)

Publication of the International Union Against Cancer

ASSOCIATION OF BODY SIZE AND FAT DISTRIBUTION WITH RISK OF BREAST CANCER AMONG CHINESE WOMEN

Xiao-Ou SHU[1]*, Fan JIN[2], Qi DAI[1], Jian Rong SHI[3], John D. POTTER[4], Louise A. BRINTON[5], James R. HEBERT[3], Zhixian RUAN[2], Yu-Tang GAO[2] and Wei ZHENG[1]

[1]*Vanderbilt Center for Health Service Research and Vanderbilt-Ingram Cancer Center, Vanderbilt University, Nashville, TN, USA*
[2]*Department of Epidemiology, Shanghai Cancer Institute, Shanghai, People's Republic of China*
[3]*Department of Epidemiology and Biostatistics, University of South Carolina and South Carolina Cancer Center, Columbia, SC, USA*
[4]*Fred Hutchinson Cancer Research Center, Seattle, WA, USA*
[5]*Environmental Epidemiology Branch, National Cancer Institute, Bethesda, MD, USA*

Most previous studies addressing the association of body size, weight change and body fat distribution with the risk of breast cancer were conducted in Western societies with a high proportion of overweight people. It remains unclear whether the dose-response relation observed in earlier studies can be extended to women with "normal" weight based on prevailing Western standards. To address this issue, we analyzed data from a population-based case-control study of breast cancer recently completed among Chinese women in urban Shanghai. In-person interviews and anthropometric measurements were completed for 1,459 women newly diagnosed with breast cancer from 25 to 64 years of age and 1,556 controls frequency-matched to cases on age. Unconditional logistic regression was employed to estimate adjusted odds ratios (ORs) and 95% confidence intervals (CI) related to anthropometric variables and self-reported body weight. Currently measured weight, body mass index [BMI: weight (kg)/height(m)^2] or height was each found to be positively related to risk of postmenopausal breast cancer in a dose-response manner, with ORs (95% CI) being 2.0 (1.4–3.0), 2.0 (1.2–3.2) or 1.7 (1.2–2.5), respectively, for the highest category of weight, BMI or height compared to the lowest category of these variables. These variables were unrelated to premenopausal breast cancer risk. Reported weight at ages >40 years and weight gain after age 20 were more predictive for postmenopausal breast cancer than weight at an earlier age. After adjustment for BMI, waist-to-hip ratio was related to an increased risk of premenopausal [OR = 1.7 (1.3–2.3) for the highest category compared to the lowest category] but not postmenopausal breast cancer. This study suggests that, even in a relatively thin Chinese population, weight gain and height are related to an increased risk of postmenopausal breast cancer, while central fat distribution was associated with premenopausal breast cancer. General weight control may be an effective measurement for breast cancer prevention.

Key words: *obesity, fat distribution, breast cancer*

Obesity has been found to be associated with an increased risk of breast cancer among postmenopausal women and unrelated to or related to a reduced risk of breast cancer risk among premenopausal women in many epidemiological studies.[1–13] The association of body fat distribution with breast cancer has not been well characterized. It has been suggested that central obesity, mainly measured by the waist-to-hip ratio, is positively associated with an increased risk of breast cancer among all women,[14–17] among postmenopausal women[18–21] and among premenopausal women.[13] The vast majority of published results were based on studies conducted in Western countries where the prevalence of obesity is high. Only a limited number of studies have been conducted to evaluate breast cancer risk in populations in which a vast majority of women are classified as thin or of normal weight according to the standard used in Western societies.[9,22,23] Thus, it remains unclear whether the dose-response relation between body size and breast cancer risk observed in overweight population could be extended to those of "normal" weight.

Chinese women traditionally have a low breast cancer risk. The incidence of breast cancer among Chinese women in Shanghai is only one-third that of American women. However, a more than 80% increase in breast cancer incidence has been reported during the last 2 decades among younger Chinese women.[24] Chinese women also have a low prevalence of obesity, thus providing an opportunity to evaluate the association of weight, fat distribution and body size with breast cancer risk among women of normal weight. We report here the association of current anthropometry and report weight history with the risk of pre- and postmenopausal breast cancer risk using data collected in a recently completed Shanghai Breast Cancer Study.

MATERIAL AND METHODS

The Shanghai Breast Cancer Study is a population-based case-control study.[25] All study subjects were permanent residents of urban Shanghai who had no prior history of cancer and were alive at the time of interview. Eligible cases included all women newly diagnosed with breast cancer during the period August 1996–March 1998 and who were from the ages of 25–64 years. Through a rapid case-ascertainment system, supplemented by the population-based Shanghai Cancer Registry, 1,602 eligible breast cancer cases were identified during the study period, and in-person interviews were completed for 1,459 (91.1%) of them. The major reasons for nonparticipation were refusal (109 cases, 6.8%), death prior to interview (17 cases, 1.1%) and inability to locate (17 cases, 1.1%). All diagnoses were confirmed by 2 senior pathologists through the review of slides.

Controls were randomly selected from female permanent residents in urban Shanghai and frequency-matched to cases by age (5-year interval). The number of controls in each age-specific stratum was determined in advance according to the age distribution of the incident breast cancer cases reported to the Shanghai Cancer Registry from 1990–1993. The Shanghai Resident Registry, which keeps registry cards for all permanent residents in urban Shanghai, was used to select controls. For each of those 1990–1993 cases, a registry card identifying a potential control in the same 5-year age group was randomly selected. A woman was considered eligible for the study only if she had lived at the

Grant sponsor: National Cancer Institute; Grant number: USPHS RO1CA64277.

*Correspondence to: Vanderbilt University School of Medicine, Center for Health Service Research, 6th floor, Medical Center East, Nashville TN 37232-8300, USA. Fax: +615-936-1269.
E-mail: Xiao-Ou.Shu@mcmail.vanderbilt.edu

Received 11 January 2001; Revised 17 April 2001; Accepted 4 June 2001

TABLE I – COMPARISON OF CASES AND CONTROLS ON DEMOGRAPHICS AND SELECTED BREAST CANCER RISK FACTORS, THE SHANGHAI BREAST CANCER STUDY, 1996–1998

	Cases[1] (n = 1459)	Controls[1] (n = 1556)	p-value
Age (%)			
25–34	2.9	5.3	
35–44	35.9	36.4	
45–54	38.7	33.4	
55–64	22.5	24.9	<0.01
Education (%)			
No formal education	3.6	5.5	
Elementary school	8.5	8.4	
Middle + high school	74.3	75.4	
Profession, college and above	13.6	10.7	0.01
Per capita income (Yuan) (%)			
<4,000	19.8	18.2	
4,000–5,999	31.7	31.9	
6,000–7,999	13.0	13.9	
8,000–8,999	20.2	23.5	
≥9,000	15.2	12.4	0.05
Breast cancer in first-degree relatives (%)	3.7	2.4	0.05
Ever had breast fibroadenoma (%)	9.6	5.0	<0.01
Regular alcohol drinker (%)	4.0	4.1	0.99
Ever used oral contraceptives (%)	21.9	20.9	0.51
Ever used hormone replacement therapy (%)	2.9	2.7	0.76
Menarcheal age (years)	14.5 ± 1.6	14.7 ± 1.7	<0.01
Menopausal age[2] (years)	48.1 ± 4.6	47.5 ± 4.9	0.02
Nulliparous (%)	5.1	3.9	0.13
Number of live births[3]	1.5 ± 0.85	1.5 ± 0.86	0.54
Age at first live birth[3] (years)	26.8 ± 4.2	26.2 ± 3.9	<0.01
Months of breastfeeding[4]	15.1 ± 13.1	15.9 ± 14.0	0.81
Energy intake (kcal/day)	1,865.9 ± 464.2	1,839.9 ± 464.2	0.12
Total fat intake (g/day)	36.3 ± 17.4	35.3 ± 16.2	0.08
Exercise regularly (%)	18.8	25.2	<0.01

Subjects with missing values were excluded from the analysis.–[1]Unless otherwise specified, mean ± SD are presented.–[2]Among menopausal women.–[3]Among women who had live births.–[4]Among women who ever breastfed.

TABLE II – ASSOCIATION BETWEEN ANTHROPOMETRIC MEASUREMENTS AND RISK OF BREAST CANCER[1]

	Premenopausal women					Postmenopausal women				
	Cases (n = 952)		Controls (n = 990)		OR[1] (95% CI)	Cases (n = 501)		Controls (n = 562)		OR[1] (95% CI)
	No.	%	No.	%		No.	%	No.	%	
Current weight at diagnosis (kg)										
<52	208	21.9	239	24.2	1.0	74	14.8	122	21.7	1.0
52–56.9	210	22.1	239	24.2	1.0 (0.7–1.3)	87	17.4	106	18.9	1.4 (0.9–2.2)
57–63.9	289	30.5	285	28.8	1.1 (0.8–1.4)	150	30.0	172	30.6	1.6 (1.1–2.3)
≥64	242	25.5	226	22.8	1.0 (0.8–1.4)	189	37.8	162	28.8	2.0 (1.4–3.0)
Trend test					p-value = 0.52					p-value < 0.0001
Height (cm)										
<155	145	15.3	162	16.4	1.0	132	26.4	195	34.7	1.0
155–158.9	265	27.9	252	25.5	1.2 (0.9–1.6)	148	29.5	163	29.0	1.2 (0.9–1.7)
159–161.9	202	21.3	241	24.4	1.0 (0.7–1.3)	106	21.2	103	18.3	1.6 (1.1–2.4)
≥162	337	35.5	334	33.7	1.2 (0.9–1.6)	115	22.9	101	18.0	1.7 (1.2–2.5)
Trend test					p-value = 0.52					p-value = 0.001
BMI at diagnosis										
<20.70	231	24.3	281	28.4	1.0	63	12.6	98	17.5	1.0
20.70–22.79	254	26.8	282	28.5	1.1 (0.8–1.4)	95	19.0	117	20.8	1.4 (0.9–2.1)
22.80–25.09	253	26.7	234	23.7	1.2 (0.9–1.6)	134	26.8	153	27.2	1.5 (1.0–2.3)
25.10–27.90	159	16.7	142	14.4	1.1 (0.8–1.5)	125	25.0	121	21.5	1.7 (1.1–2.6)
≥28.0	52	5.5	50	5.0	1.1 (0.7–1.7)	83	16.6	73	13.0	2.0 (1.2–3.2)
Trend test					p-value = 0.34					p-value = 0.003
WHR at diagnosis										
<0.764	217	22.9	299	30.2	1.0	66	13.2	89	15.9	1.0
0.764–0.79	250	26.3	264	26.7	1.4 (1.1–1.8)	95	19.0	126	22.4	0.9 (0.6–1.4)
0.80–0.834	243	25.6	232	23.5	1.4 (1.1–1.8)	142	28.3	148	26.3	1.3 (0.8–1.9)
0.835–0.864	134	14.1	117	11.8	1.6 (1.2–2.2)	88	17.6	108	19.2	1.1 (0.7–1.6)
≥0.865	105	11.1	77	7.8	1.8 (1.3–2.6)	110	21.9	91	16.2	1.6 (1.0–2.5)
Trend test					p-value < 0.001					p-value = 0.014

[1]Adjusted for age, education, family history of breast cancer, ever had fibroadenoma, age at menarche, age at first live birth, exercise and age at menopause for menopausal women.

TABLE III – ASSOCIATION BETWEEN OBESITY, FAT DISTRIBUTION AND RISK OF BREAST CANCER[1]

WHR at diagnosis	Premenopausal women's (cases 952; controls 990) BMI at diagnosis				ORs adjusted for BMI	WHR at diagnosis	Postmenopausal women's (cases 501; controls 562) BMI at diagnosis				ORs adjusted for BMI
	<20.70	20.70–22.79	22.80–25.09	≥25.10			<20.70	20.70–22.79	22.80–25.09	≥25.10	
≤0.764	1.0 (reference)	0.9 (0.6–1.4)	1.1 (0.7–1.9)	2.0 (0.9–4.3)	1.0 (reference)	≤0.764	1.0 (reference)	1.7 (0.7–4.1)	1.5 (0.6–3.9)	2.1 (0.8–5.7)	1.0 (reference)
0.765–0.8	1.4 (1.0–2.2)	1.5 (1.0–2.3)	1.5 (1.0–2.4)	1.2 (0.7–2.2)	1.4 (1.1–1.8)	0.765–0.8	0.9 (0.4–2.2)	1.8 (0.8–4.0)	0.8 (0.4–1.8)	1.3 (0.6–3.0)	0.8 (0.5–1.2)
0.81–0.835	1.5 (0.8–2.5)	1.6 (1.0–2.6)	1.4 (0.9–2.2)	1.3 (0.8–2.1)	1.4 (1.1–1.8)	0.81–0.835	0.9 (0.3–2.7)	1.0 (0.4–2.3)	2.9 (1.4–6.2)	2.2 (1.0–4.6)	1.1 (0.7–1.6)
>0.835	2.6 (1.2–5.9)	1.8 (1.1–3.1)	2.0 (1.3–3.2)	1.5 (1.0–2.2)	1.7 (1.3–2.3)	>0.835	1.2 (0.5–3.3)	1.9 (0.8–4.4)	1.4 (0.7–2.9)	2.2 (1.1–4.4)	1.1 (0.7–1.6)
ORs adjusted for WHR	1.0 (reference)	1.0 (0.8–1.3)	1.1 (0.8–1.4)	0.9 (0.7–1.2)		ORs adjusted for WHR	1.0 (reference)	1.5 (0.9–2.3)	1.5 (1.0–2.3)	1.9 (1.2–2.9)	

[1]Adjusted for age, education, family history of breast cancer, ever had fibroadenoma, age at menarche, age at first live birth, exercise and age at menopause for menopausal women.

registered address during the study period. In-person interviews were completed for 1,556 (90.3%) of the 1,724 eligible controls identified. Reasons for nonparticipation included refusal (166 controls, 9.6%) and death or a prior cancer diagnosis (2 controls, 0.1%).

All study participants were interviewed by trained interviewers at hospitals (cases) or at home (cases and controls). A structured questionnaire was used to elicit detailed information on demographic factors, menstrual and reproductive history, hormone use, dietary habits, prior disease history, physical activity, tobacco and alcohol use, weight history and family history of cancer. Information on body size included perceived weight and height compared to peers at ages 10, 15 and 20 years, weight at age 20 years, and each decade afterward, as well as weight during the year prior to the interview.

All participants were measured by trained interviewers according to a standard protocol for their current weight, circumferences of the waist and hip and sitting and standing heights. Waist circumferences were measured at 2.5 cm above the navel and hip circumferences at the level of maximum width of the buttocks. All measurements were taken twice with a tolerance limit of 1 kg for weight and 1 cm for heights and circumferences. A third measurement was taken if the difference of the 2 measurements was greater than the tolerance limit. The averaged measurements were used in this analysis.

Quartile distributions among controls were applied to categorize anthropometric variables. Given that our study participants in general had a low waist-to-hip ratio (WHR) and body mass index (BMI) compared to women in Western countries, we have further divided our 4th quartile of WHR and BMI into 2 categories to facilitate intrastudy comparisons. Odds ratios (OR) were used to measure the association of breast cancer risk with body size and weight changes. Unconditional logistic regression models were used in the analysis to obtain maximum likelihood estimates of the odds ratios and their 95% confidence intervals (CI), after adjusting for potential confounders.[26] Age was included as a continuous variable throughout data analyses, and categorical variables were treated as dummy variables in the model. Tests for trend were performed by entering the categorical variables as continuous parameters in the models. All analyses were performed using SAS, and all tests of statistical significance were 2-sided.

RESULTS

Table I presents comparisons of cases and controls on demographic factors and traditional breast cancer risk factors, as well as usual caloric (energy in kcal/day) and total fat intake. Compared to controls, cases were slightly older (mean ages 47.8 years for cases and 47.3 years for controls), more likely to have a higher education, a family history of breast cancer among first-degree relatives and a history of breast fibroadenoma. Cases had earlier age at menarche, later age at menopause, later age at first live birth and were less likely to have participated in regular exercise than controls. All subsequent analyses included the above potential confounding variables in logistic regression models. There was no significant case-control difference in parity, duration of breastfeeding, family income (after adjustment for education), alcohol consumption, use of oral contraceptives, hormone replacement therapy or usual caloric and fat intake.

Among postmenopausal women, both current weight and height were positively associated with the risk of breast cancer (p for trend both < 0.001) (Table II). Compared to women less than 52 kg, women of 64 kg or heavier had a 2-fold increased risk of breast cancer (95% CI = 1.4–3.0), after adjustment for nonanthropometric risk factors. The association was slightly attenuated (OR = 1.9, 95% CI = 1.3–2.9) after further adjustments for height. Being 162 cm in height or taller also was associated with increased risk (OR = 1.7, 95% CI = 1.2–2.5). Weight and height, however, were not related to the risk of breast cancer among premenopausal women.

TABLE IV – WEIGHT AND WEIGHT CHANGE DURING ADULTHOOD AND RISK OF BREAST CANCER[1]

	Premenopausal women			Postmenopausal women		
	Cases 952 (%)	Controls 990 (%)	OR (95% CI)	Cases 501 (%)	Controls 562 (%)	OR (95% CI)
Weight at 20 years (kg)						
<45	19.8	21.9	1.0	22.6	21.9	1.0
45–48.9	27.1	26.3	1.1 (0.8–1.5)	27.0	25.8	0.8 (0.6–1.3)
49–52.9	25.7	26.0	1.0 (0.8–1.4)	25.0	27.8	0.7 (0.5–1.1)
≥53	37.4	25.8	1.1 (0.8–1.5)	25.4	24.5	0.8 (0.5–1.2)
Trend test	p-value = 0.67			p-value = 0.17		
Weight at 30 years (kg)						
<47.5	20.4	22.3	1.0	20.2	24.5	1.0
47.5–51.9	27.4	25.7	1.2 (0.9–1.5)	29.6	27.9	1.3 (0.9–1.8)
52–57.4	26.1	26.2	1.0 (0.8–1.4)	24.2	23.3	1.2 (0.8–1.7)
≥57.5	26.1	25.8	1.0 (0.8–1.4)	26.0	24.3	1.2 (0.8–1.8)
Trend test	p-value = 0.91			p-value = 0.58		
Weight at 40 years (kg)						
<50	18.3	18.0	1.0	17.6	24.9	1.0
50–54.9	22.7	24.1	1.0 (0.7–1.4)	25.5	24.0	1.5 (1.0–2.2)
55–59.9	23.4	21.8	1.0 (0.7–1.5)	20.6	20.3	1.3 (0.9–2.0)
≥60	35.6	36.1	0.9 (0.6–1.2)	36.4	30.8	1.7 (1.1–2.5)
Trend test	p-value = 0.52			p-value = 0.033		
Weight at 50 years (kg)						
<51	17.7	15.7	1.0	15.4	24.5	1.0
51–57.9	23.8	19.1	1.1 (0.4–2.9)	27.3	27.6	1.6 (1.1–2.5)
58–63.9	28.5	28.1	1.0 (0.4–2.4)	26.2	23.8	1.9 (1.2–3.0)
≥64	30.0	37.1	0.9 (0.4–2.4)	31.1	24.1	2.1 (1.3–3.3)
Trend test	p-value = 0.78			p-value = 0.003		
Weight at 60 years (kg)						
<52.5				17.1	23.8	1.0
52.5–59.9				22.7	23.3	1.5 (0.8–3.1)
60–64.9				20.4	22.3	1.2 (0.6–2.5)
≥65				39.8	30.6	1.7 (0.8–3.3)
Trend test				p-value = 0.24		
Weight gain since age 20 (kg)						
<1.15	22.2	23.4	1.0	20.4	28.0	1.0
1.15–3.41	23.1	20.8	1.1 (0.8–1.5)	31.7	32.4	1.4 (1.0–2.1)
3.42–5.64	26.9	23.7	1.1 (0.8–1.4)	26.6	28.0	1.3 (0.9–1.9)
≥5.65	27.8	32.1	1.0 (0.8–1.3)	21.3	11.6	2.7 (1.7–4.2)
Trend test	p-value = 0.80			p-value < 0.001		
Weight gain during past 10 years (kg)						
<1.15	28.5	30.4	1.0	37.1	46.2	1.0
1.15–3.41	15.4	15.4	1.1 (0.8–1.5)	19.8	16.4	1.6 (1.1–2.2)
3.42–5.64	17.6	15.7	1.2 (0.9–1.6)	14.3	13.4	1.2 (0.8–1.8)
≥5.65	38.5	38.5	1.1 (0.9–1.4)	28.8	24.0	1.5 (1.1–2.1)
Trend test	p-value = 0.42			p-value = 0.03		

[1]Adjusted for age, education, family history of breast cancer, ever had fibroadenoma, age at menarche, age at first live birth, exercise and age at menopause for menopausal women.

Similarly, BMI [weight (kg)/height(m)^2] was associated with an increased risk of breast cancer only among postmenopausal women but not in premenopausal women (Table II). BMI greater than 28 was associated with an OR of 2.0 (95% CI = 1.2–3.2) in postmenopausal women and an OR of 1.1 (95% CI = 0.7–1.7) in premenopausal women.

Both waist and hip circumferences were positively associated with the risk of breast cancer among pre- and postmenopausal women (data not shown). When breast cancer risk was assessed in relation to the WHR, a dose-response relationship was observed for both pre- and postmenopausal women (Table II).

Because BMI and WHR are moderately correlated in these data (r = 0.33), further analyses were conducted to identify the independent association between BMI and WHR and breast cancer risk (Table III). No association between BMI and risk of premenopausal breast cancer risk was observed in most strata defined by WHR. On the other hand, WHR was directly associated with breast cancer risk among premenopausal women in each category of BMI, with the exception of overweight or obese women (BMI ≥ 25.10). Among postmenopausal women, however, BMI was directly associated with the risk of breast cancer, whereas WHR was unrelated.

Table IV presents the association between risk of breast cancer and self-reported weight history at different decades of life and weight change. Neither weight at different periods of life nor weight change since age 20 or during the previous 10 years was related to the risk of premenopausal breast cancer risk. Weight at the age of 20 and 30 years also was not related to the risk of breast cancer among postmenopausal women. However, weight in later life, particularly during the perimenopausal period (*i.e.*, ages 40 and 50), was directly positively associated with postmenopausal breast cancer. Further analysis showed that weight gain since age 20 and during the previous 10 years were both positively associated with postmenopausal breast cancer risk, although a higher risk was found for the former. A similar pattern was observed when levels of BMI in different decades of life were examined (data not shown), with an exception of a higher BMI (≥ 21.11) at age 20 being related to a significantly lower risk of postmenopausal breast cancer (OR = 0.6, 95% CI = 0.4–0.9).

To examine the joint and independent effect of weight gain and BMI at age 20, additional analyses were conducted (Table V). Neither weight gain since age 20 nor BMI at age 20 was related to the risk of premenopausal breast cancer. Weight gain since age 20, however, was related to an increased risk of postmenopausal breast cancer across all strata of BMI at age 20, and the positive association appeared to be stronger among women who had a lower BMI

TABLE V – ASSOCIATION OF BMI AT AGE 20 AND WEIGHT GAIN SINCE AGE 20 AND RISK OF BREAST CANCER[1]

	Premenopausal women's (cases 952; controls 990) weight gain since age 20 (kg)			ORs adjusted for weight gain since age 20		Postmenopausal women's (cases 501; controls 562) weight gain since age 20 (kg)			ORs adjusted for weight gain since age 20
	<1.15	1.15–5.64	≥5.65			<1.15	1.15–5.64	≥5.65	
BMI at age 20					BMI at age 20				
<17.69	1.0 (reference)	1.4 (0.6–3.4)	1.3 (0.5–2.9)	1.0 (reference)	<17.69	1.0 (reference)	3.1 (0.9–11.0)	4.6 (1.2–17.4)	1.0 (reference)
17.69–19.28	1.6 (0.6–4.1)	1.4 (0.6–3.3)	1.3 (0.5–3.2)	1.0 (0.8–1.4)	17.69–19.28	1.5 (0.3–6.3)	2.3 (0.7–7.9)	5.6 (1.4–22.5)	0.9 (0.6–1.3)
19.29–21.10	1.2 (0.5–2.8)	1.6 (0.7–3.7)	1.3 (0.5–3.1)	1.0 (0.8–1.4)	19.29–21.10	1.7 (0.5–6.4)	2.6 (0.7–9.0)	6.2 (1.5–25.6)	1.0 (0.6–1.5)
≥21.11	1.4 (0.6–3.3)	1.4 (0.6–3.4)	1.3 (0.5–3.7)	1.1 (0.8–1.4)	≥21.11	1.8 (0.5–6.5)	2.1 (0.6–7.5)	3.0 (0.6–14.5)	0.8 (0.5–1.3)
ORs adjusted for BMI at age 20	1.0 (reference)	1.1 (0.9–1.4)	1.0 (0.7–1.3)		ORs adjusted for BMI at age 20	1.0 (reference)	1.4 (1.0–2.0)	2.8 (1.7–4.5)	

[1]Adjusted for age, education, family history of breast cancer, ever had fibroadenoma, age at menarche, age at first live birth, exercise and age at menopause for postmenopausal women.

at age 20 [*e.g.*, the ORs of breast cancer associated with weight gain ≥5.65 kg compared to weight gain <1.15 kg were 4.6 (4.6/1), 3.7 (5.6/1.5), 3.6 (6.2/1.7) and 1.7 (3.0/1.8), respectively, for the lowest to highest quartile stratum of BMI at age 20]. The OR of postmenopausal breast cancer associated with weight gain of 5.65 kg or more since age 20 was 2.8 (95% CI = 1.7–4.5) after adjusting for BMI at age 20. BMI at age 20 was not associated with postmenopausal breast cancer after adjusting for weight gain.

DISCUSSION

This population-based case-control study, conducted in a population at a low risk of breast cancer and a low prevalence of obesity, found that weight, height and BMI were related to the risk of postmenopausal but not premenopausal breast cancer. On the other hand, WHR was positively associated with both premenopausal and postmenopausal breast cancer but after adjustment for BMI, WHR was only associated with an increased risk of premenopausal breast cancer. Also, among postmenopausal women, weight gain since age 20 and weight in later life, particularly during the perimenopausal period, were more closely related to breast cancer risk than was weight in early adult life.

There exist substantial international variations in the incidence of breast cancer, as well as in body weight and height. Both height and weight have been found to be highly correlated with breast cancer incidences on a worldwide basis, although the weight-breast cancer association was attenuated after adjustment for height.[27] The height-breast cancer association also has been observed in many retrospective and prospective studies, although the evidence is not entirely consistent.[28] In our study, height was related to breast cancer risk among postmenopausal women but not premenopausal women. Height is determined by many variables including genetic factors and energy balance during childhood and adolescence, which is determined largely by caloric intake. The influence of caloric intake on height is more important in societies with an insufficient food supply than those with an abundant food supply. A larger proportion of postmenopausal women than premenopausal women in our study population grew up in periods when supplies of energy were insufficient. Among controls of our study, there was a substantially high proportion (34.7%) of shorter (high <155 cm) and a lower proportion (18.0%) of taller (>162 cm) women among postmenopausal women compared to premenopausal women (the respective percentages are 16.4% and 33.7% for height <155 cm and >162 cm), suggesting that the differential effect of height on breast cancer by menopausal status found in our study might be due to the general low energy intake during adolescence among postmenopausal women. In our study, consumption of rice and wheat products, the major source of energy in the study population, during adolescence was negatively associated with the risk of breast cancer,[29] providing further support to the energy deprivation in early life hypothesis. However, height also was associated with an increased risk of breast cancer among women in the United States and other developed nations where most women grew up with abundant energy supply.[5,7,8,16,30–37] Thus, factors other than energy balance may also be involved in the association between height and breast cancer. Inherited patterns in endogenous hormones and growth factors that contribute to the height attained prior to epiphyseal closure at puberty and also to the promotion of breast carcinogenesis has been hypothesized as one of the explanations.[28] This hypothesis, however, does not explain why the association of height with breast cancer differs by menopausal status found in our study.

Consistent with many earlier studies,[1,4,5,7,11] we found that weight and BMI were directly associated with an increased risk of postmenopausal breast cancer, an association that persisted after adjustment for WHR. When self-reported weight history was examined, it appeared that weight after age 40 and weight gain since age 20 were better predictors than current weight for postmenopausal breast cancer. This finding is consistent with those observed in the United States and European countries.[5,10,35,37–39] In the large

cohort study of nurses, Huang *et al.*[10] found that the weight gain and postmenopausal breast cancer association was confined to women who never used estrogen replacement therapy. It is noteworthy that the vast majority of women in our study are nonpostmenopausal estrogen users (97.1% and 97.3% for cases and controls, respectively). Excluding the 3% postmenopausal estrogen users from analysis did not alter the association of weight gain with postmenopausal breast cancer. In our study, we also found that weight gain is the main player in the inverse association of BMI at age 20 with postmenopausal breast cancer, a finding similar to that of the Iowa Women's Health Study[38] but disagree with that of the Nurse's Health Study.[10] Our findings are biologically plausible since weight gain during adulthood is accounted for largely by an increase in fat tissue, and excess body fat has been found to increase extra-ovarian production of estrogen and decrease sex hormone-binding globulin among postmenopausal women.[40,41] We did not find that weight, weight gain or BMI was related to breast cancer risk among premenopausal women. This might be due to the much higher ovarian hormone concentrations among premenopausal women that override the effect of estrogen produced by excess fat.

In our study, we found that fat distribution, measured by WHR, was related to the risk of premenopausal breast cancer. We did not find an independent association of WHR with postmenopausal breast cancer risk after adjustment of BMI. Results from earlier studies on WHR and breast cancer have been inconsistent. Some reported an association in both pre- and postmenopausal women[16,17] and others found an association depending on menopausal status (postmenopausal cancer;[18–21] premenopausal breast cancer[13]). Others even reported no significant association.[11,34,42] WHR has been found to be associated with higher levels of androgens, insulin and reduced levels of sex hormone-binding globulin,[41,43–45] factors that have been previously linked with breast cancers risk.[44,46–48] While all these nonestrogenic profile changes associated with high WHR are likely to increase the risk of breast cancer, further studies are needed to better understand the association of WHR and breast cancer, particularly with regard to menopausal status and the underlying mechanism(s).

Our study has a number of strengths. First, the population-based case-control study design and high participation rate (91%) minimized selection bias. Second, anthropometric measurements were taken by trained interviewers using a standard protocol, and this was done for most cancer cases within days of diagnosis, thus reducing measurement errors and some of the effects of therapy on body weight. Third, the prevalence rate of obesity in the study population is low, allowing an assessment of the association of body fat and fat distribution with breast cancer risk in closer to an ideal normal weight range according to the standards of Western populations. Our study, however, cannot avoid some of the inherent limitations of the case-control design. For example, the weight histories may reflect the influence of recall bias, although these were more likely to be nondifferential with respect to case-control status.

In summary, our study found that weight gain since age 20 and being overweight at a later age were associated with an increased risk of postmenopausal breast cancer among normal or slightly overweight women, indicating that weight control may be an effective measure for breast cancer prevention for postmenopausal women. High waist-to-hip ratio was linked to an elevated risk of premenopausal breast cancer, emphasizing the need for future research to define mechanisms other than estrogen-mediated in relation to breast cancer by menopausal status and to determine the genetic and environmental influences on body fat distribution.

REFERENCES

1. Lubin F, Ruder AM, Wax Y, et al. Overweight and changes in weight throughout adult life in breast cancer etiology. Am J Epidemiol 1985;122:579–88.
2. Willett WC, Brown MD, Bain BC, et al. Relative weight and risk of breast cancer among premenopausal women. Am J Epidemiol 1985; 122:731–40.
3. Marchand LL, Kolonel LN, Earle ME, et al. Body size at different periods of life and breast cancer risk. Am J Epidemiol 1988;128:137–52.
4. Chu SY, Lee NC, Wingo PA, et al. The relationship between body mass and breast cancer among women enrolled in the cancer and steroid hormone study. J Clin Epidemiol 1991;44:1197–206.
5. Brinton LA, Swanson CA. Height and weight at various ages and risk of breast cancer. Ann Epidemiol 1992;2:597–609.
6. Pathak DR, Whittemore AS. Combined effects of body size, parity, and menstrual events on breast cancer incidence in seven countries. Am J Epidemiol 1992;135:153–68.
7. Radimer K, Siskind V, Bain C, et al. Relation between anthropometric indicators and risk of breast cancer among Australian women. Am J Epidemiol 1993;138:77–89.
8. Ballard-Barbash R. Anthropometry and breast cancer. Cancer 1994; 74:1090–100.
9. Chie W-C, Chen C-F, Lee W-C, et al. Body size and risk of pre- and post-menopausal breast cancer in Taiwan. Anticancer Res 1996;16: 3129–32.
10. Huang Z, Hankinson SE, Colditz GA, et al. Dual effects of weight and weight gain on breast cancer risk. J Am Med Assoc 1997;278:1407–11.
11. Franceschi S, Favero A, Vecchia EL, et al. Body size indices and breast cancer risk before and after menopause. Int J Cancer 1996;67: 181–6.
12. Trentham-Dietz A, Newcomb PA, Storer BE, et al. Body size and risk of breast cancer. Am J Epidemiol 1997;145:1011–9.
13. Sonnenschein E, Toniolo P, Terry MB, et al. Body fat distribution and obesity in pre-and postmenopausal breast cancer. Int J Epidemiol 1999;28:1026–31.
14. Schapira DV, Kumar NB, Lyman GH, et al. Abdominal obesity and breast cancer risk. Ann Intern Med 1990;112:182–6.
15. Ballard-Barbash R, Schatzkin A, Taylor PR, et al. Association of change in body mass with breast cancer. Cancer Res 1990;50:2152–5.
16. Mannisto S, Pietinen P, Pyy M, et al. Body-size indicators and risk of breast cancer according to menopause and estrogen-receptor status. Int J Cancer 1996;68:8–13.
17. Ng E-H, Gao F, Ji C-Y, et al. Risk factors for breast carcinoma in Singaporean Chinese women. Am Cancer Soc 1997;80:725–31.
18. Bruning PF, Bonfrer JM, Hart AA, et al. Body measurements, estrogen availability and the risk of human breast cancer: a case-control study. Int J Cancer 1992;51:14–9.
19. Kaaks R,Van Noord PA, Den Tonkelaar I, et al. Breast-cancer incidence in relation to height, weight and body-fat distribution in the Dutch "DOM" cohort. Int J Cancer 1998;76:647–51.
20. Folsom AR, Kushi LH, Anderson KE, et al. Associations of general and abdominal obesity with multiple health outcomes in older women: the Iowa Women's Health Study. Arch Intern Med 2000;160:2117–28.
21. Hall IJ, Newman B, Millikan RC, et al. Body size and breast cancer risk in black women and white women: the Carolina Breast Cancer Study Am J Epidemiol 2000;151:754–64.
22. Yuan JM, Yu MD, Ross RK, et al. Risk factors for breast cancer in Chinese women in Shanghai. Cancer Res 1988;48:1949–53.
23. Yang PS, Yang TL, Liu CL, et al. A case-control study of breast cancer in Taiwan—a low-incidence area. Br J Cancer 1997;75:752–6.
24. Jin F, Devesa S, Chow W, et al. Cancer incidence trends in urban Shanghai, 1972–1994: an update. Int J Cancer 1999;83:435–40.
25. Gao YT, Shu XO, Dai Q, et al. Menstrual, reproductive factors and breast cancer risk in urban Shanghai, People's Republic of China. Int J Cancer 2000;87:295–300.
26. Breslow NE, Day NE. Statistical methods in cancer research. Vol. 1. The analysis of case-control studies. Lyon: International Agency for Research on Cancer, 1980.
27. Albanes D, Taylor PR. International differences in body height and weight and their relationship to cancer incidence. Nutr Cancer 1990; 14:69–77.
28. Ziegler RG. Anthropometry and breast cancer. J Nutr 1997;127:924S–928S.
29. Shu XO, Jin F, Dai Q, et al. Soyfood intake during adolescence and subsequent risk of breast cancer among Chinese women. Cancer Epidemiol Biomark Prevent, 2001;10:483–8.
30. Swanso CA, Jones DY, Schatzkin A, et al. Breast cancer risk assessed by anthropometry in the NHANES I epidemiological follow-up study. Cancer Res 1988;48:5363–7.
31. Tretli S. Height and weight in relation to breast cancer morbidity and

mortality. A prospective study of 570,000 women in Norway. Int J Cancer 1989;44:23–30.
32. London SJ, Colditz GA, Sampfer MJ, et al. Prospective study of relative weight, height, and risk of breast cancer. J Am Med Assoc 1989;262:2853–8.
33. Palmer JR, Rosenberg L, Harlap S, et al. Adult height and risk of breast cancer among U.S. black women. Am J Epidemiol 1995;141: 845–9.
34. Swanson CA, Coates RJ, Schoenberg JB, et al. Body size and breast cancer risk among women under age 45 years. Am J Epidemiol 1996;143:698–706.
35. Ziegler RG, Hoover RN, Nomura AMY, et al. Relative weight, weight change, height, and breast cancer risk in Asian-American women. J Natl Cancer Inst 1996;88:650–60.
36. Van Den Brandt PA, Dirx MJ, Ronckers CM, et al. Height, weight change, and postmenopausal breast cancer risk: the Netherlands Cohort Study. Cancer Causes Control 1997;8:39–47.
37. Magnusson C, Baron J, Persson I, et al. Body size in different periods of life and breast cancer risk in post-menopausal women. Int J Cancer 1998;76:29–34.
38. Barnes-Josiah D, Potter JD, Sellers TA, et al. Early body size and subsequent weight gain as predictors of breast cancer incidence (Iowa, United States). Cancer Causes Control 1995;6:112–8.
39. Trentham-Dietz A, Newcomb PA, Egan KM, et al. Weight change and risk of postmenopausal breast cancer (United States). Cancer Causes Control 2000;11:533–42.
40. Siiteri PK. Adipose tissues as a source of hormones. Am J Clin Nutr 1987;45:277–82.
41. Kaye SA, Folsom AR, Soler JT, et al. Associations of body mass and fat distribution with sex hormone concentrations in postmenopausal women. Int J Epidemiol 1991;20:151–6.
42. Huang Z, Willett WC, Colditz GA, et al. Waist circumference, waist: hip ratio, and risk of breast cancer in the Nurses' Health Study. Am J Epidemiol 1999;150:1316–24.
43. Bruning PF. Endogenous estrogens and breast cancer: a possible relationship between body fat distribution and estrogen availability. J Steroid Biochem 1987;27:487–92.
44. Bruning PF, Bonfrer JM, Van Noord PA, et al. Insulin resistance and breast-cancer risk. Int J Cancer 1992;52:511–6.
45. Dorgan JF, Reichman ME, Judd JT, et al. The relation of body size to plasma levels of estrogens and androgens in premenopausal women (Maryland, United States). Cancer Causes Control 1995;6:3–8.
46. Toniolo PG, Levitz M, Zeleniuch-Jacquotte A, et al. A prospective study of endogenous estrogens and breast cancer in postmenopausal women. J Natl Cancer Inst 1995;87:190–7.
47. Dorgan JF, Longcope C, Stephenson HE Jr., et al. Relation of prediagnostic serum estrogen and androgen levels to breast cancer risk. Cancer Epidemiol Biomarkers Prev 1996;5:533–9.
48. Del Giudice ME, Fantus IG, Ezzat S, et al. Insulin and related factors in premenopausal breast cancer risk. Breast Cancer Res Treat 1998; 47:111–20.